An electronic thesaurus of Evidence Based Laboratory Medicine hematological and biochemical diagnostic tests

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SUMMARY

The adoption of Evidence Based Laboratory Medicine (EBLM) has been hampered until today by the lack of effective tools. The SIMeL EBLM e-Thesaurus (on-line Repertoire of the diagnostic effectiveness of the laboratory, radiology and cardiology test) provides a useful support to clinical laboratory professionals and to clinicians for the interpretation of the diagnostic tests. The e-Thesaurus is an application developed using Microsoft® Active Server Pages technology and carried out with Web Server Microsoft® Internet Information Server and is available at the SIMeL website using a browser running JavaScript® scripts (Internet Explorer® is recommended). It contains a database (in Italian, English and Spanish) of the sensitivity and specificity (including the 95% confidence interval), the positive and negative likelihood ratios, the Diagnostic Odds Ratio and the Number Needed to Diagnose of more than 2000 diagnostic (most laboratory but also cardiology and radiology) tests. The e-Thesaurus improves the previous SIMeL paper and CD Thesaurus; its main features are a three languages search and a continuous and an easy updating capability.

INTRODUCTION

Sensitivity (Sens) and specificity (Spec), according to the Evidence Based Laboratory Medicine (EBLM), allow to calculate positive (LR+) and negative likelihood ratios (LR−) that can be used for obtaining the post-test probability from the pretest probability (Guyatt & Rennie, 2002; Price & Christenson, 2003; Straus *et al.*, 2005; Christenson, 2007). This is very important because the clinician needs to know, from the practical point of view, the probability of disease once the carried out test yields positive or negative results, i.e. the information power of the test. In this regard, it can also be useful to have tools for objectively comparing different laboratory tests. LR+ and LR− are well known parameters and can be easily calculated using respectively the formulas: Positive likelihood ratio (LR+) = Sens/(1−Spec) and negative likelihood ratio (LR−) = (1−Sens)/Spec. An LR+ value = 6 indicates that an individual with the condition has six times higher probability to have a positive result compared to an individual without the condition while an LR− value = 0.1 indicates that an individual with the condition has 10 times lower probability to have a negative result compared to an individual without the condition (Brown & Reeves, 2003; Deeks & Altman, 2004). It is easy to obtain the post-test probability by using the nomogram proposed by Fagan which simplifies very much the calculation (Fagan, 1975). The post-test odds can be obtained by multiplying the pretest odds, that can be calculated from the ratio of the prevalence and the reciprocal of the prevalence and the LR. Furthermore, the post-test odds/(post-test odds + 1) × 100 gives the post-test probability. Guyatt *et al*. (1992) showed in their classical study on ferritin use in anaemia diagnosis that the pretest odds in the case of a 31% prevalence was 0.45 (31%/69%); the LR+ of six in their report yielded a post-test odds of 2.7 and a post-test probability of 2.7/3.7 = 73%. The LRs present clear advantages compared with Sens and Spec; their use is easier, they can be calculated for different concentrations and can be used in a sequential manner (the post-test probability after a first test becoming the pretest probability of a second test). For example, when a 45-year-old patient consults a physician, has a 6% pretest probability of >75% stenosis of at least one coronary (Sackett *et al.*, 2000). The LR for coronary stenosis if he reports an atypical chest pain is 13 and if he has a ST-segment depression is 11. In this case, the final post test odds are 9.13 [(0.06/0.94) × 13 × 11] and the post-test probability is 9.13/10.13 = 90%. There is a growing feeling that the LRs could improve the interaction of laboratorians with clinicians and could provide a tool for the clinical audit since the diagnostic power of the tests requested by the clinician can be assessed and compared (Christenson, 2007).

In 2001, the EBLM Group of the SIMeL produced, in order to provide the colleagues with a tool useful for their everyday practice of EBLM: a booklet containing a Thesaurus of diagnostic (most laboratory, but also cardiology and radiology) tests (Dorizzi, Giavarina & Esposito, 2006). The volume contained the diagnostic efficiency parameters of more than 1000 tests extracted from 33 references (most from a textbook published in 1989) (Goldenberg, Verdain Barnes & Redding, 1989), that, notwithstanding its pocket size, was not fully handy. Furthermore, the search could be made only by test, the volume had a high cost, contained some typographical mistakes and could not be updated. A second (CD) edition of Thesaurus, published in 2006, contained an expanded data base [more than 2000 tests with diagnostic odds ratio (DOR) and number needed to diagnose (NND) values extracted from more than 100 sources] and allowed a keyword-based search (Dorizzi & Giavarina, 2001). The CD had a high cost, contained some typographical mistakes and, according to some users, was complex to operate. Therefore, the SIMeL launched the project of a web version of the EBLM e-Thesaurus (on-line Repertoire of the diagnostic effectiveness of the laboratory, radiology and cardiology test) which could overcome the limits of the previous versions and that could be freely accessible by clinical laboratory professionals and by clinicians. The aim of this study was to summarize the main features of this project.

MATERIALS AND METHODS

The on-line Thesaurus is easily searched in three languages (Italian, English and Spanish) through powerful full-text search functions and is being continuously updated in real-time. The SIMeL wants to promote the EBLM. Therefore, the access to the SIMeL EBLM e-Thesaurus will be allowed, in a preliminary phase, by simply accessing to the website of

the Society (www.simel.it) and entering demo as User and Password in the Login (Figure 1).

The operation of the e-Thesaurus is very simple: language can be chosen by clicking on the proper flag and a search function allows to search more than 2000 laboratory, radiology and cardiology tests entering a whole term or a part of it (the symbol % can be used for wildcard) relative to a test or to a disease.

For example, the search LEUKOCYTES (Figure 2) yields the results shown in Figure 3: the columns of the table contain information about (from left to right): Firm (when available); Pathology/Disease and cut-off (when available); Sens and its 95% Confidence Interval (when available); Spec and its 95% confidence interval (when available); LR+; LR−; DOR; NND and Reference that yielded the data. The authors of this electronic thesaurus selected the data of interest in Textbooks and in papers; in all the cases the DOR and the NND have been calculated using the formulas described respectively by Glas *et al.* and by Batstone and the Excel™ Microsoft spreadsheet.

The LRs allow to integrate the result of a diagnostic test with the clinical judgment about the probability of a diagnosis in a specific patient. The integration can be made through the calculations of Bayes' Theorem or, much more simply, through nomograms and algorithms. The SIMeL EBLM e-Thesaurus employs an interactive modified version of the Fagan nomogram based on three vertical axes: left (pretest probability); central (likelihood ratio) and right (post-test probability). When the e-Thesaurus user clicks on the LR+ or LR− of the selected test, the LR-value is automatically

Figure 1. The homepage of Italian Society of Laboratory Medicine (SIMeL) website.

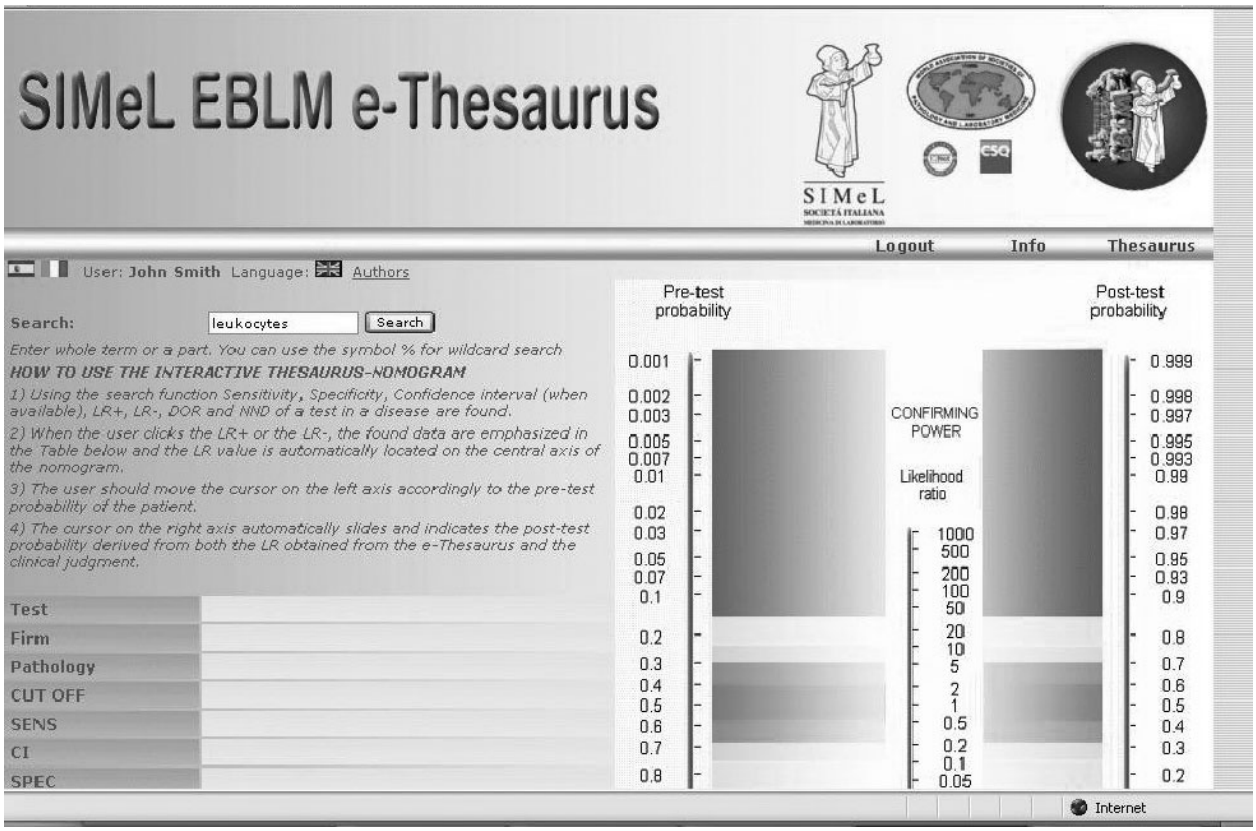
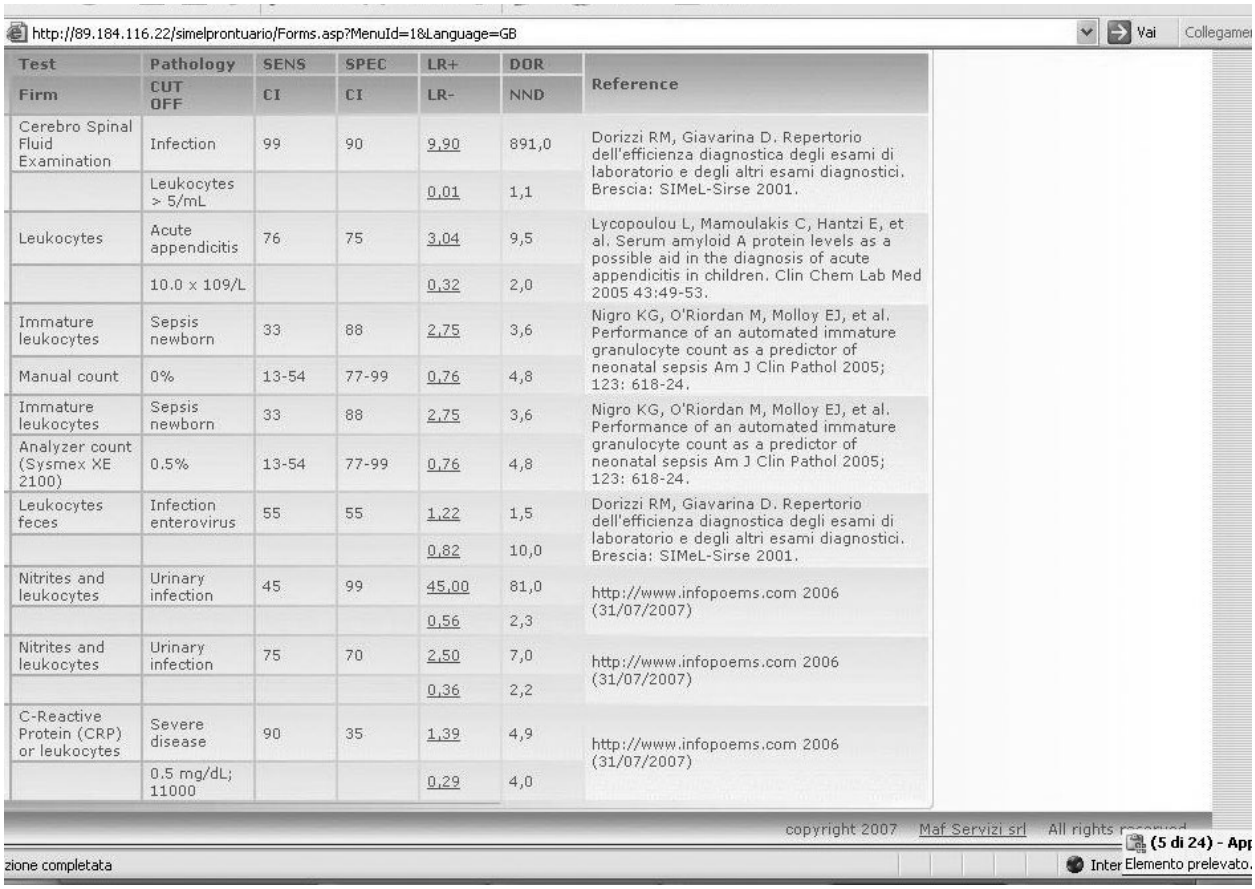


Figure 2. Example of a search in the SIMeL EBLM e-Thesaurus using the keyword LEUKOCYTES.

transferred on the central axis of the nomogram (Figure 4). Once the user selects the pretest probability appropriate for the patient on the left axis in accordance with, the cursor on the right axis accordingly and simultaneously moves and indicates the post-test probability (Figure 5). The user will be immediately able to assess how much the post-test probability changes when pretest probability increases or decreases.

The e-Thesaurus has been developed using the Microsoft® Internet Information Server (IIS) web server and the technology used for writing the applications carried out by the ISS is Microsoft® Active Server Pages (ASP). In summary, the application is made of particular documents generating HTLM codes for the user's browser. For example, when the term 'AFP' is searched in the e-Thesaurus, the browser of the user queries one ASP page in the server and receives the HTLM page containing the found data. When the user clicks on an LR-value, a local codex is activated on his/her browser which accordingly localizes the cursor on the central axis of the nomogram. The codex serving this interaction is called client type (since it is carried out in the user side) and uses the Java script language which is supported by all the browsers. Internet Explorer™ is recommended for this application because is the most used and is, at the present and most probably will be in the future, supported by the producer (Microsoft®). It should be noted that, while the e-Thesausus can be employed without any additional plug-ins by most of the Windows users, it is not compatible with Macintosh™ machines.

The e-Thesaurus can be easily updated in real time. According to the authors, the source code of the toolkit could be useful to the e-Thesaurus users; therefore, they are considering its placement in the public domain. However, in a preliminary phase, a more restricted use of the source code better protects the property rights of the Author who developed the



http://89.184.116.22/simelprontuario/Forms.asp?MenuId=1&Language=GB

Test / Firm	Pathology / CUT OFF	SENS / CI	SPEC / CI	LR+ / LR-	DOR / NND	Reference
Cerebro Spinal Fluid Examination	Infection	99	90	9,90	891,0	Dorizzi RM, Giavarina D. Repertorio dell'efficienza diagnostica degli esami di laboratorio e degli altri esami diagnostici. Brescia: SIMeL-Sirse 2001.
	Leukocytes > 5/mL			0,01	1,1	
Leukocytes	Acute appendicitis	76	75	3,04	9,5	Lycopoulou L, Mamoulakis C, Hantzi E, et al. Serum amyloid A protein levels as a possible aid in the diagnosis of acute appendicitis in children. Clin Chem Lab Med 2005 43:49-53.
	10.0 x 109/L			0,32	2,0	
Immature leukocytes	Sepsis newborn	33	88	2,75	3,6	Nigro KG, O'Riordan M, Molloy EJ, et al. Performance of an automated immature granulocyte count as a predictor of neonatal sepsis Am J Clin Pathol 2005; 123: 618-24.
Manual count	0%	13-54	77-99	0,76	4,8	
Immature leukocytes	Sepsis newborn	33	88	2,75	3,6	Nigro KG, O'Riordan M, Molloy EJ, et al. Performance of an automated immature granulocyte count as a predictor of neonatal sepsis Am J Clin Pathol 2005; 123: 618-24.
Analyzer count (Sysmex XE 2100)	0.5%	13-54	77-99	0,76	4,8	
Leukocytes feces	Infection enterovirus	55	55	1,22	1,5	Dorizzi RM, Giavarina D. Repertorio dell'efficienza diagnostica degli esami di laboratorio e degli altri esami diagnostici. Brescia: SIMeL-Sirse 2001.
				0,82	10,0	
Nitrites and leukocytes	Urinary infection	45	99	45,00	81,0	http://www.infopoems.com 2006 (31/07/2007)
				0,56	2,3	
Nitrites and leukocytes	Urinary infection	75	70	2,50	7,0	http://www.infopoems.com 2006 (31/07/2007)
				0,36	2,2	
C-Reactive Protein (CRP) or leukocytes	Severe disease	90	35	1,39	4,9	http://www.infopoems.com 2006 (31/07/2007)
	0.5 mg/dL; 11000			0,29	4,0	

Figure 3. The hits yielded of the search LEUKOCYTES in the e-Thesaurus.

toolkit (CG) and the further developing and testing of the Thesaurus (its Portuguese version is now in preparation). At the moment, only the administrators of the Thesaurus are being allowed to update the database; on the contrary, all the interested colleagues worldwide can freely contact the corresponding author for possible future collaborations.

RESULTS AND DISCUSSION

The odds ratio is a familiar statistic in epidemiology, expressing the strength of association between exposure and disease (Glas *et al.*, 2003) but is a much less known indicator of test performance in laboratory medicine. The DOR of a test is the ratio of the odds of positivity in disease relative to the odds of positivity in the nondiseased. Alternatively, the DOR can be read as the ratio of the odds of disease in test positives relative to the odds of disease in test negatives. As such, it also can be applied to express the strength of the association between test result and disease. In our opinion, however, the DOR could be really useful in dichotomous and especially in assessing polychotomous tests. Lin *et al.* (1989) showed, for example, that cut off ranging from 180 to 900 U/l yielded a DOR ranging from 147 to 561. There is a close relation between the DOR and the LRs, and DOR can be easily calculated from the ratio LR+/LR−. The value of a DOR ranges from 0 to infinity, with higher values indicating better discriminatory test performance. A value of 1 means that a test does not discriminate between patients with the disorder and those without it. The DOR as a measure of test performance, combines the strengths of sensitivity and specificity, as prevalence independent indicators, with the advantage of being a single indicator. Whenever false

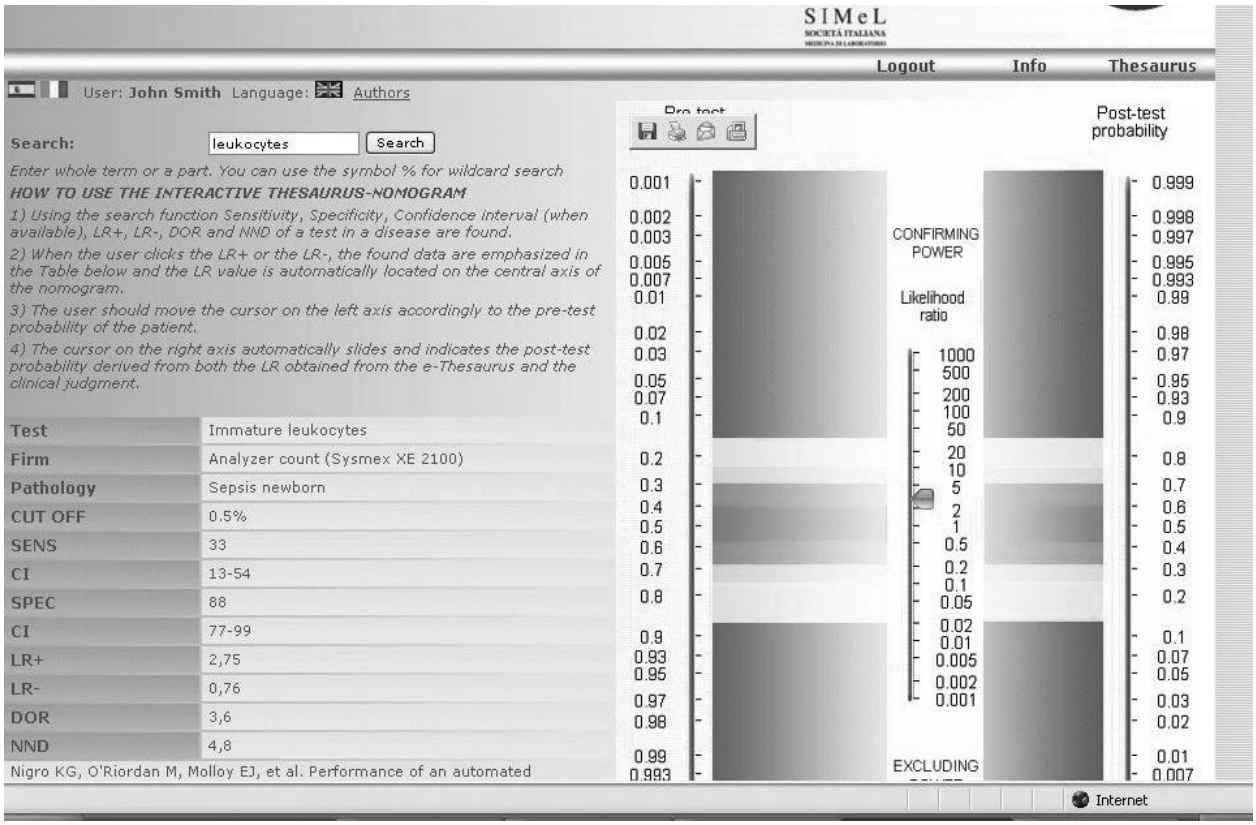


Figure 4. Example of how the LR+ value is automatically transferred to the Fagan's nomogram of the Thesaurus.

positives and false negatives are weighted differentially, both the prevalence and the conditional error rates of the test have to be taken into consideration to make a balanced decision. In these cases, the DOR is less useful, as it does not distinguish between the two types of diagnostic mistake. Really, a test with a 0.99 specificity and an 0.5 sensitivity has the same DOR (99) of a test with a 0.5 specificity and a 0.99 sensitivity (Deeks, 2001). Therefore, if we need to rule-out or rule-in the target condition is the primary intended use of a test, conditional indicators such as Sens and Spec still have to be used. A very sensitive assay is needed for ruling out a disease (SnNOut) and a very specific test is needed for ruling in a disease (SpPIn) (Sackett *et al.*, 2000). A further parameter recently proposed is the NND which is similar to the Number Needed to Treat (NNT, the reciprocal of the fractional improvement in a treated group minus the fractional improvement in an untreated group) (Batstone, 1997; Reid & Galloway, 1998; Sintchenko & Gilbert, 1998). For a diagnostic test, the analogous calculation of a NND would be the reciprocal of the fraction of positive tests in the group with the disease minus the fraction of positive tests in the group without the disease, i.e. NND = 1/[Sensitivity−(1−Specificity)]. The NND indicates the number of tests which need to be undertaken in order to gain a positive response for the presence of disease and permits a ready comparison between tests. It is regretful that even if Batstone (1997) effectively showed 10 years ago that staining *Helicobacter pylori* was more effective compared with IgA antibodies (NND = 1.08 *vs.* 1.64), the NNDs are really very little used in Laboratory literature.

The SIMeL e-Thesaurus is on-line since 20th August 2007 and is being operated since then by colleagues in several parts of the world. We think that several interesting and important results have been obtained, since the e-Thesaurus:

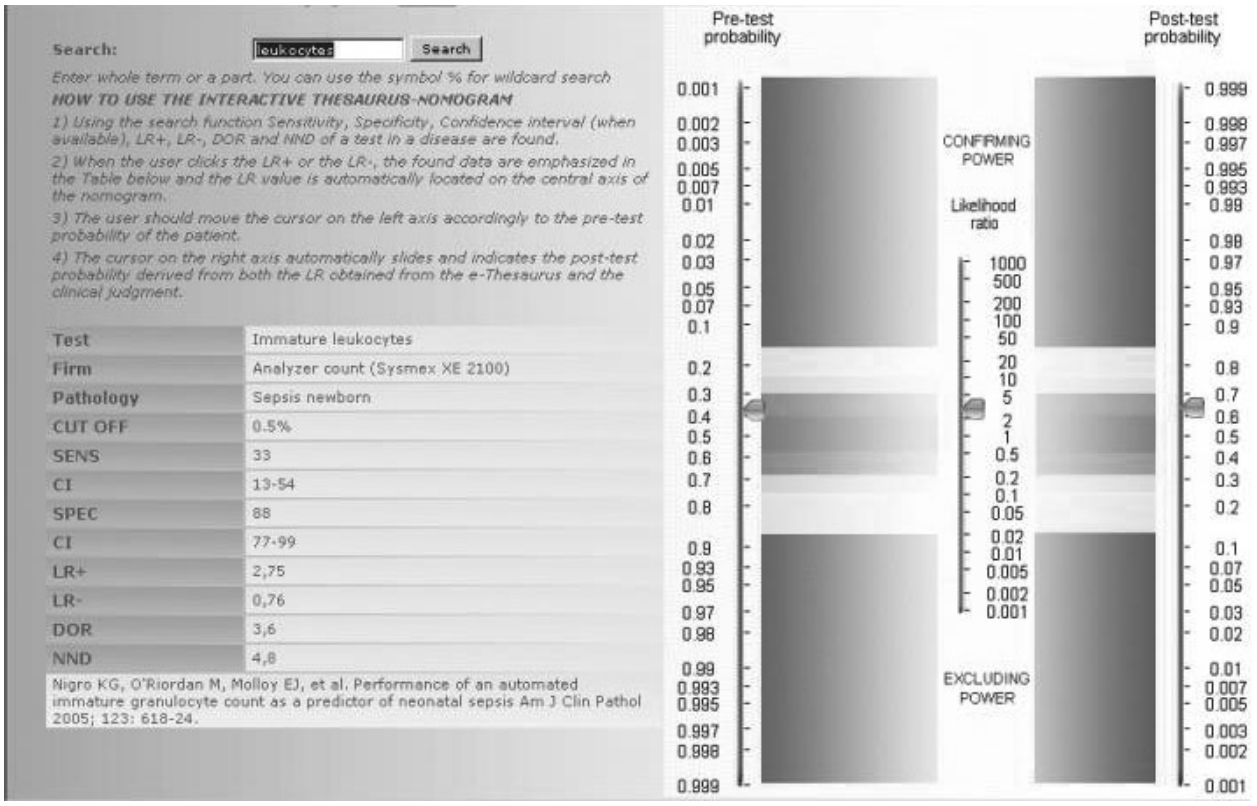


Figure 5. Example of an automatic estimation of the post-test probability once the user chooses the pretest probability.

- is, at our knowledge, the unique interactive electronic database containing the greatest amount of evidence-based information about diagnostic tests;
- contains EBLM advanced parameters such as DOR and NND which, in our opinion, deserve to be more known and used by both laboratorians and clinicians;
- is based on a very advanced informatics technology that allows graphical results much more elegant and effective than, for example, the interactive nomogram available at the Oxford Centre for Evidence Based Medicine website (14). A relevant feature is the precise meaning of the colour code of the nomogram: a test with an LR falling in the red area is totally useless since the LR is around 1; one with an LR falling in the green area it is useful, while one a LR falling in areas with intermediate colours, has an intermediate usefulness;
- operates without any plug-in and requires only a PC equipped with Internet Explorer;
- presents a database architecture which allows a virtually unlimited very easy and fast update of the database even in specialistic fields such as endocrinology and haematology. In this regard, the articles published by Journals recognizing and accepting the STARD criteria will be preferred in order to rapidly improve the overall quality of the database.

We hope that the e-Thesaurus will become soon widely used not only in Italy but also abroad and its English and Spanish versions will help in this regard. Finally, the interactive nomogram could be easily used for teaching purposes since the user could instantaneously appreciate how much the post-test probability changes when the pretest probability changes. Really, the graphical approach could be really helpful in Bayesian reasoning not only to laboratorians and clinicians but also to students.

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